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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,357	03/21/2001	De-Chao Yu	348022001600	3927

24353 7590 04/02/2003

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	21

DATE MAILED: 04/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,357	YU ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59,60,62,63,72-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59,60,62,63,72-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *30 January 2003* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 59, 60, 62, 63, 72-79 are pending examination.

Applicants' traversal; the amendment to claims 59, 62, and 75-76; the cancellation of claims 61 and 64-71; the addition of claims 77-79 in paper no 20. is acknowledged and considered.

Election/Restrictions

This application contains claims 59 and 75 drawn to a nonelected species without traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected species or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claims 59 and 75 remain objected to because of the following informalities: claims read on non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Applicants arguments, see paper no.20, filed 1/30/03 with respect to 112 first paragraph enablement rejection have been fully considered and are persuasive. The rejection of claims 59-63, 65-66, and 72-76 has been withdrawn because the specification teaches intravenous and intra-tumoral administration of the adenoviral vector to reduce tumor growth of a tumor in a mammal and the cancellation of claims 65-66.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 59, 60, 62, 63, and 72-75 remain and claims 76-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59, 60, 62, 63, and 72-75 remain and claims 76-79 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is: what is the target of the adenovirus vector and how is the adenovirus vector suppressing tumor growth in an individual if the claim does not define where it is being administered. The claim is indefinite because the claim does not complete the pre-amble, which encompasses a method for suppressing tumor growth in an individual. Suggest inserting the phrase -- to a mammal -- after the word "administering" on line 2 of each independent claim.

Applicants' arguments filed 1/30/03 have been fully considered but they are not persuasive. Applicants did not provide any arguments for the above 112 second paragraph rejection.

Claim Rejections - 35 USC § 103

Applicant's arguments, see pages 5-6 of paper no. 20, filed 1/30/03, with respect to 103(a) rejection as unpatentable over Henderson taken with Kim have been fully considered and

are persuasive. The rejection of claims 59, 61, 66, and 72-73 as unpatentable over Henderson taken with Kim has been withdrawn because applicants removed cisplatin from the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 60, 62, 63, and 72-73 remain and claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with

Gurnani et al. (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999). Henderson teaches a method for suppressing tumor growth comprising introducing an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). Furthermore, Henderson teaches that the adenovirus gene essential for propagation is the adenoviral early gene, E1A or E1A and E1B (columns 10- 11 and column 15). Henderson further teaches using intravenous or intra-tumoral injection of the adenovirus to treat a tumor in a mammal (column 25, lines 1-23). The adenovirus, which is transcriptionally competent in target cells, may be used to kill the cells. To further ensure cytotoxicity, one may have one or more transgenes present, which have cytotoxic effect. In this way one can provide high confidence that the target cells will be destroyed while providing for the appropriate level of expression of the cytotoxic agents. However, Henderson does not teach specifically teach a combination method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-specific TRE and an anti-neoplastic agent selected from the group consisting of paclitaxel, docetaxel, doxorubicin, and etoposide, at a dose level effective for suppressing tumor growth when administered alone.

However, at the time the invention was made, Gurnani teaches that p53 adenovirus combined with doxorubicin, paclitaxel, methotrexate, or etoposide inhibited cell proliferation more effectively than chemotherapy alone (pages 145-150). Gurnani teaches using doxorubicin (4mg/kg) and etoposide at amounts that are contemplated by the specification for suppressing

tumor growth at a dose less than the effective does for suppressing tumor growth when administered alone (see pages 49-50 of the specification for the concentration range of alkaloids used in chemotherapy).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use the adenoviral vector taught by Henderson in the combination method for suppressing a tumor in a mammal taught by Gurnani. One of ordinary skill in the art would have been motivated to use the replication competent adenovirus vector taught by Henderson in the method taught by Gurnani because Henderson teaches that replication competent adenoviral vectors may be used for its cytotoxic effect and because the replication competent adenoviral vector would be restricted to target cells compared to the replication defective adenoviral vector taught by Gurnani. In addition, Henderson teaches that the adenovirus can comprise a transgene to further ensure the cytotoxicity of the cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/30/03 have been fully considered but they are not persuasive. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. In view of the totality of the prior art, one of ordinary skill in the art would have been motivated to use the adenoviral vector taught by Henderson in the method taught by Gurnani because using the replication competent adenoviral vector in the method taught by Gurnani would result an

improved method of inhibiting the growth of cancer cells compared to using the replication defective adenovirus taught by Gurnani. Furthermore, the breadth of the claim embraces using an adenovirus comprising a transgene and Henderson teaches to further ensure the cytotoxicity of the cells a transgene can be inserted in the adenovirus vector.

Claims 59, 73, and 74 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson (US Patent No. 5,871,726) taken with Gurnani (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999) in further view of Duque (Cancer Gene Therapy, Vol. 6, pp. 554-563, 1999).

The rejection of the base claims 59 and 73 under 35 U.S.C. 103(a) is applied here as indicated above, by Henderson taken with Gurnani. However, Henderson taken with Gurnani does not teach specifically teach a combination method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-specific TRE, wherein the gene essential for replication is the adenoviral early gene E1B with a deletion of the 19-kDa region and an alkaloid at a dose less than the effective does for suppressing tumor growth when administered alone.

However, at the time the invention was made, Duque teaches that 19-kDa and 55-kDa E1B-deficient adenovirus induced marked cytopathic effect on malignant cells that was higher than that seen for wild type adenovirus (abstract). In addition, such adenovirus exerts a tumor suppressor effect *in vivo*. Duque teaches the 19-kDa protein in adenovirus inhibits the apoptotic pathway induced by expression of the Ad E1a protein (page 555).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to modify the adenovirus taught by Henderson as taught by Duque and use the modified adenovirus in the combination method for suppressing tumor growth in a tumor in a mammal taught by Gurnani. One of ordinary skill in the art would have been motivated to modify the adenovirus by deleting the 19-kDa region and using the modified vector in combination with any alkaloid in a method of suppressing growth of a tumor cell in a mammal because Duque teaches that deleting the 19-kDa region can induce a higher cytopathic effect in malignant cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/30/03 have been fully considered but they are not persuasive for the reasons set forth above. Applicants have not added any new arguments other than the arguments set forth in the previous 103(a) rejection.

Furthermore, in response to applicants' argument that the references fail to show certain features of applicants' invention, it is noted that the features upon which applicants rely (i.e., synergistic effect) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 75 remains and claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Chiang et al. (WO 97/10007, IDS). Henderson teaches a method for suppressing tumor growth comprising introducing an

adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). The adenovirus, which is transcriptionally competent in target cells, may be used to kill the cells, while optionally producing one or more proteins of interest. However, Henderson does not specifically teach a method for suppressing tumor growth in a mammal comprising administering a replication competent adenoviral vector and external radiation at a dose less than the effective dose for suppressing tumor growth when administered alone.

However, at the time the invention was made, Chiang teaches a process for improving the treatment of tumor by radiation therapy which comprises treating a tumor by radiation therapy wherein the cells have been transfected with a polynucleotide encoding a wild type p53, such as for example by transducing the cells with an adenoviral vector comprising a DNA sequence encoding wild-type p53 (abstract, pages 1, 3, 21, 34-37). Chiang teaches using radiation therapy at a dose less than the effective dose for suppressing tumor growth when administered alone, 1.8 to 2.25 Gy (see page 160 of the as-filed specification).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use the adenoviral vector taught by Henderson in the method taught by Chiang. One of ordinary skill in the art would have been motivated to use the adenoviral vector taught by Henderson in the method of suppressing a tumor cell of a mammal because Henderson teaches the advantages of using a replication competent adenoviral vector (e.g., using competent adenovirus allows for proliferation of the adenovirus in the target cells resulting in the

death of the host cells and proliferation of the adenovirus to other host cells) compared to using a replication defective adenoviral vector.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 1/30/03 have been fully considered but they are not persuasive. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. Using the combination therapy would have obvious to one ordinary skill in the art because of the improved effect of using the adenoviral vector taught by Henderson in the treatment of tumor cells taught by Chiang.

Furthermore, the assertion (one of skill in the art could not have predicted that adenovirus would be able to successfully replicate in cells that are undergoing radiation therapy as the cellular metabolism is severely disrupted under these conditions, see page 7 of paper no. 20) made by the applicants is moot because the applicants have not provided factual evidence that a replication competent adenovirus can not be used with radiation therapy to treat tumors in a mammal and because the specification supports that not all tumor are susceptible to radiation. The specification states, "Tumors and tissue themselves are also characterized by a range of susceptibilities to radioactive therapy. Lymphoma and leukemias are very sensitive to radiation therapy, while renal cancer and gland tumors are fairly insensitive to radiation." (see page 6). Thus, one of ordinary skill in the art would have been motivated to use the combination method

taught by Henderson taken with Chiang to improve the treatment of tumor cells not fully susceptible to radiation.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER